Modulation of beta-catenin function maintains mouse epiblast stem cell and human embryonic stem cell self-renewal.

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Public Summary:
In this study, we uncovered a novel mechanism by which human embryonic stem cells and mouse epiblast stem cells retain their pluripotency, or ability to differentiate into virtually any kind of cell. We found that Wnt/beta-catenin signaling pathway—a group of molecules that work together to control various cell functions, can prompt human embryonic stem cells and mouse epiblast stem cells to either self-renew or differentiate. When the protein beta-catenin remains within the cell cytoplasm but outside of the nucleus, the stem cell continues to self-renew. When beta-catenin moves into a stem cell's nucleus, differentiation begins. Our study will advance our efforts to better control stem cell fate, which is critical to the future of regenerative medicine.

Scientific Abstract:
Wnt/beta-catenin signalling has a variety of roles in regulating stem cell fates. Its specific role in mouse epiblast stem cell self-renewal, however, remains poorly understood. Here we show that Wnt/beta-catenin functions in both self-renewal and differentiation in mouse epiblast stem cells. Stabilization and nuclear translocation of beta-catenin and its subsequent binding to T-cell factors induces differentiation. Conversely, retention of stabilized beta-catenin in the cytoplasm maintains self-renewal. Cytoplasmic retention of beta-catenin is effected by stabilization of Axin2, a downstream target of beta-catenin, or by genetic modifications to beta-catenin that prevent its nuclear translocation. We also find that human embryonic stem cell and mouse epiblast stem cell fates are regulated by beta-catenin through similar mechanisms. Our results elucidate a new role for beta-catenin in stem cell self-renewal that is independent of its transcriptional activity and will have broad implications in understanding the molecular regulation of stem cell fate.